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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,462	09/30/2005	Junichi Masuyama	081356-0250	4423

22428 7590 06/18/2008

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
06/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,462	MASUYAMA ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-30-05 11-26-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group II and election of species filed March 7, 2008 is acknowledged.

   Claims 1-26 are pending.

   Applicant's election without traverse of Group II, drawn to a method for inducing differentiation and/or promoting proliferation of a regulator T cell, and the species method that is performed "ex vivo" in the reply filed on March 7, 2008 is acknowledged.

   Accordingly, claim 1-11 and 24-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 7, 2008.

   Moreover, claims 12-23 are under examination as they read on a method for inducing differentiation and/or promoting proliferation of a regulator T cell, and the species method that is performed "ex vivo".

2. Signed copies of the Information Disclosure Statements filed September 30, 2005 and November 26, 2007 are attached.

   With respect to the Information Disclosure Statements filed September 30, 2005, applicant requests each listed document be considered by the Examiner and made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609. However, applicant has not provided copies of the cited references for the examiners consideration as evidenced by the Form PCT/DO/EO/903 mailed to applicant on July 11, 2006. Applicant must follow the procedure set forth in 37 CFR 1.97 and 1.98 in order to ensure that the examiner considers the documents cited in the international search report. See MPEP § 1893.03(g).

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(a)-(d) and papers submitted under 35 U.S.C. 119(a)-(d) filed September 30, 2005 are acknowledged.

   However, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a)-(d) as follows:

   The filing date of the foreign priority documents are not perfected unless applicant has filed a certified priority document in the application and an English language translation (see 37 CFR 1.55(a)(3)) such that the examiner can establish that the priority documents satisfies the enablement and description requirements of 35 U.S.C. 112, first paragraph.

Accordingly, the instant claims will be given the benefit of priority as of March 31, 2004 in the examination that follows.

4. Claim 23 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim in that it is dependent from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 12-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 reads on a method employing a CD52 agonist "other than a 4C8 antibody".

The phrase "other than a 4C8 antibody" is not explicitly defined by the instant specification and it would be unclear to the skilled artisan what this phrase refers to.

Potential interpretations of the phrase "other than a 4C8 antibody" include: "other than the particular 4C8 mAb described in Masuyama et al. (Masuyama, J. et al., (2002) J. Immunol., 169, 3710)," or "other than any antibody that binds to 4C8."

Note that according to the teachings of the instant specification, any antibody that binds to the 4C8 antigen will also bind CD52 since the instant specification asserts these molecules are one in the same (see instant specification, page 10, last paragraph).

Thus, if "other than a 4C8 antibody" means "other than any antibody that binds to 4C8" then it also necessarily means "other than any antibody that binds to CD52".

However, many of the claims that depend from claim 12 are drawn to methods employing anti-CD52 antibodies which seems to contradict this interpretation of the phrase "other than a 4C8 antibody" of claim 12.

Also, claim 16 is drawn to an anti-CD52 antibody called "campath-1H". Claim 16 is indefinite in the recitation of "campath-1H" as the means of identifying this rat anti-CD52 antibody because this term is merely a laboratory designation which does not clearly define the claimed antibody. Different laboratories may use the same designations to define distinct biological materials.

However, it appears from the teachings of the instant specification as well as the art, see e.g., Bloom et al. (Am J Transplant. 2008 Apr;8(4):793-802), that at least one "campath-1H"

antibody is the anti-CD52 antibody which has been in clinical use in the United States since 2001 and is known by the international non-propriety name "alemtuzumab" as designated by the Work Health Organization (see, e.g., instant specification at page 18, 1st paragraph).

If applicant intends to claim the "alemtuzumab" in claim 16, amending the claim to substitute "alemtuzumab" for "campath-1h" would overcome the rejection as it pertains to the recitation of "campath-1h" in claim 16.

In conclusion, the instant claims fail to particularly point out and distinctly set forth the subject matter which applicant regards as the invention, and as a consequence the metes and bounds of the claimed invention are so unclear as to preclude the skilled artisan from ascertaining what would infringe the instantly claimed invention should it issue as a patent.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 12-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing the differentiation and/or promoting the proliferation of a CD4+ T cell with the ability to suppress the proliferation of a CD4-positive or CD8-positive T cells in a CD4-positive- or CD8-positive-T-cell mixed lymphocyte culture reaction which comprises: (a) isolating CD4+ T cells, (b) culturing said CD4+ T cells of step (a) on a plate to which an anti-CD52 agonistic antibody and an anti-CD3 antibody have been immobilized, or (c) isolating CD4+ T cells, (d) culturing CD4+ T cells of step (c) on a plate to which an anti-CD52 agonistic antibody has been immobilized and which further comprises monocyte-derived mature dendritic cells allogenic to said cultured CD4+ T cells, and wherein following steps (b) or (d), CD4+ T cells with the ability to suppress the proliferation of CD4-positive-T-cells or CD8-positive-T-cells in a CD4-positive- or CD8-positive-T-cell mixed lymphocyte culture reaction comprising CD4-positive- or CD8-positive-T-cells and allogenic monocyte-derived mature dendritic cells are formed ***does not reasonably provide enablement for*** a method for inducing differentiation and/or promoting proliferation of a regulatory T cell, which comprises causing a CD52 agonist other than a 4C8 antibody to act on CD52 that is expressed on the surface of an immunocyte.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in

In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states on page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The knowledge in the art pertaining to inducing differentiation and/or promoting proliferation of a regulatory T cell, which comprises causing a CD52 agonist other than a 4C8 antibody to act on CD52 that is expressed on the surface of an immunocyte is low.

The instant specification discloses a method for inducing the differentiation and/or promoting the proliferation of a CD4+ T cell with the ability to suppress the proliferation of a CD4-positive or CD8-positive T cells in a CD4-positive- or CD8-positive-T-cell mixed lymphocyte culture reaction which comprises: (a) isolating CD4+ T cells, (b) culturing said CD4+ T cells of step (a) on a plate to which an anti-CD52 agonistic antibody and an anti-CD3 antibody have been immobilized, or (c) isolating CD4+ T cells, (d) culturing CD4+ T cells of step (c) on a plate to which an anti-CD52 agonistic antibody has been immobilized and which further comprises monocyte-derived mature dendritic cells allogenic to said cultured CD4+ T cells, and wherein following steps (b) or (d), CD4+ T cells with the ability to suppress the proliferation of CD4-positive-T-cells or CD8-positive-T-cells in a CD4-positive- or CD8-positive-T-cell mixed lymphocyte culture reaction comprising CD4-positive- or CD8-positive-T-cells and allogenic monocyte-derived mature dendritic cells are formed (see instant specification, in particular, pages 27-34, examples 2 and 4.1-6).

However, neither the disclosure of the instant specification, nor the knowledge in the art are sufficient for the skilled artisan to make and use the claimed invention to its full breadth.

In particular, the instant specification does not provide a working example or give sound scientific reasoning to sufficiently enable one of ordinary skill in the art to practice the claimed method to its full breadth. Rather, the substantive disclosure of the instant specification teaches a method for inducing differentiation and/or promoting proliferation of a regulatory T cell comprising causing a CD52 agonist AND a CD3 agonist to act on CD52 and CD3, respectively, that are expressed on the surface of an immunocyte.

Moreover, the teachings of the prior art indicate that practicing a method for inducing differentiation and/or promoting proliferation of a regulatory T cell comprising causing a CD52 agonist to act on CD52 that is expressed on the surface of an immunocyte is a highly unpredictable endeavor.

For example, Rowan et al. (Int Immunol. 1995 Jan;7(1):69-77, cited previously) teaches that coimmobolization of CAMPATH-1H and anti-CD3 antibodies onto plastic plates, but not coimmobolization of CAMPATH-1H and anti-CD2 or CD28, induced T cell proliferation

(see Rowan page 72, right column and Figure 2). Similarily, Rowan further teaches that CAMPATH-1H induced T cell proliferation and IL-2 production requires the crosslinking of CAMPATH-1H with an anti-Ig antibody and the presence of a T cell mitogen, such as PMA (see Rowan, page 73, left column and Table 2 and page 75, left column, 1st paragraph).

Thus, according to the teachings of Rowan, CAMPATH-1H is a T-cell co-stimulatory molecule (see, Rowan, e.g., page 76), i.e., a molecule that induces T cell proliferation and IL-2 production only in conjunction with TCR activation.

It is noted that Rowan does teach a particular rat anti-CD52 IgG2c antibody, the "YTH 361.10" antibody, can induce T cell proliferation in the absence of PMA or immobolized anti-CD3. However, this biological activity of the "YTH 361.10" rat anti-CD52 IgG2c antibody is likely a consequence of its high affinity and isotype rather than a general feature of anti-CD52 antibodies (see Rowan page 74, left column, 1st paragraph as well as Kummer et al., Eur J Immunol. 1993 Oct;23(10):2649-54). Moreover, the induction of T cell proliferation by the YTH 361.10 anti-CD52 could be increased by the presence of PMA (see Rowan paragraph bridging pages 71-72). Thus, YTH 361.10 alone is not the same as the combination of YTH 361.10 and PMA.

Furthermore, given that the instant specification discloses that Masuyama et al. (2002) J. Immunol., 169, 3710, which is incorporated by reference into the instant specification, teaches "cells activated by simultaneous stimulation with CD3 and 4C8 mAb showed in *vitro* suppressive activity upon the proliferation of CD4-positive T cells due to polyclonal stimulation, revealing that regulatory T cells had been induced," (see the instant specification at the paragraph bridging pages 1-2), and further given that the 4C8 antibody of Masuyama is an anti-CD52 antibody as taught by the instant specification in the last paragraph of page 10, the skilled artisan would look to the teachings of Masuyama to understand how to practice the claimed invention.

Like Rowan, Masuyama teaches that immobilized 4C8 antibody acting alone cannot stimulate proliferation of CD4+ T cells but that it can act as co-stimulatory agent when co-immobilized with anti-CD3 (see, e.g., the instant specification paragraph bridging pages 1-2 and Masuyama page 3712, Figure 1).

Indeed, the post-filing date publication of Bloom et al. (Am J Transplant. 2008 Apr;8(4):793-802) confirms that immobilized anti-CD52 CAMPATH-1H cannot "act on CD52 that is expressed on the surface of an immunocyte" to induce CD4+CD25+FoxP3+ regulatory T cells because according to Bloom a non-specific control human IgG antibody ("huIgG") had the same effect as immobilized anti-CD52 CAMPATH-1H acting alone on the proliferation and/or differentiation of CD4+CD25+FoxP3+ regulatory T cells (see Bloom column bridging paragraph on page 798 to right column, 2nd paragraph and Figures 7B, C and 8).

Furthermore, the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on a method for inducing differentiation and/or promoting

proliferation of a regulatory T cell wherein the phrase "a regulatory T cell," given its broadest reasonable interpretation consistent with the instant specification, reads on a variety of "regulatory T cells" known in the prior art to have a variety of different biological characteristics including differing cytokine expression abilities, e.g., TGF-β and/or IL-10 expression abilities; differing abilities to induce T cell suppression in a cell contact dependent or cell contact independent but cytokine dependent manner; and differing abilities to respond to allogenic stimulation though their TCR, i.e., T cell activation versus anergy upon stimulation with antigens (see instant specification at pages 2-7).

As stated above, given that the instant specification discloses that Masuyama et al. (2002) J. Immunol., 169, 3710, which is incorporated by reference into the instant specification, teaches "cells activated by simultaneous stimulation with CD3 and 4C8 mAb showed in vitro suppressive activity upon the proliferation of CD4-positive T cells due to polyclonal stimulation, revealing that regulatory T cells had been induced," (see the instant specification at the paragraph bridging pages 1-2), and further given that the 4C8 antibody of Masuyama is an anti-CD52 antibody as taught by the instant specification in the last paragraph of page 10, the skilled artisan would look to the teachings of Masuyama to understand how to practice the claimed invention.

According to the teachings of Masuyama, CD4+ T cells cultured in the presence of co-immobilized anti-CD3 and 4C8 (anti-CD52) antibodies give rise to 4C8-costimulated T cells with unique suppressive effects when compared to other suppressor T cells known in the prior art such as "naturally" occurring CD4+CD25+ cells that arise first in the thymus or Tr1 cells derived from naïve CD4+ T cells by repetitive stimulation in the presence of IL-10 (see Masuyama, page 3710, right column and page 3715, left column, 2nd paragraph). In contrast, Masuyama teaches that "4C8 Treg cells" mediate their suppressive functions via a cell-to-cell contact dependent mechanism independent of IL-10 or TGF-β mediated suppression, and predominately produce IL-10, but not IL-2 or IL-4, upon subsequent restimulation with immobilized anti-CD3 and anti-4C8 (see Masuyama, page 3712, right column and Table 1 and page 3714, right column and Figure 8).

Thus, the skilled artisan not be able to practice the claimed method to its full breadth in the absence of undue experimentation. This is because undue experimentation would be required to determine under what conditions, if any, anti-CD52 antibodies can induce differentiation and/or promote proliferation of a regulatory with the same properties as the regulatory T cells of the prior art such as "naturally" occurring CD4+CD25+ cells that arise first in the thymus or Tr1 cells derived from naïve CD4+ T cells by repetitive stimulation in the presence of IL-10 (see Masuyama, page 3710, right column and page 3715, left column, 2nd paragraph).

Along these same lines, neither the instant specification nor the prior art seem to indicate how the 4C8 or anti-CD52 antibody can be used by one of ordinary skill in the art to induce differentiation of a regulatory T cell, *per se*, which is another embodiment encompassed by the scope of claim 12 and dependent claims thereof.

Furthermore, claim 12, given its broadest reasonable interpretation consistent with the instant specification on reads on the use of any CD52 agonist including "natural or synthetic ligands for CD52 antigens, specifically, all molecules that induce signals via CD52 molecules." However, a review of the state of the art reveals that no naturally occurring ligand(s) for CD52 have been identified, and making a synthetic CD52 antigen, other than an anti-CD52 antibody, in the absence of any guidance or direction from the instant specification, is an unpredictable endeavor that would require undue experimentation of the skilled artisan.

For example, with respect to small organic molecules that agonize cytokine receptors, Whitty et al. (Chem. Biol. 1999 Apr;6(4):R107-18) teaches "To trigger the activation of a receptor such as GH-R by directly cross-linking two receptor chains, as illustrated in Figure 1, an agonist ligand must achieve the following: it must bind to one of the receptor chains with reasonable affinity; it must do so in a position such that additional unsatisfied binding functionality projects in the direction required for contact with a second receptor chain; it must have a sufficient affinity for the second receptor chain to shift the equilibrium for receptor dimerization to significantly favor the dimeric state of the receptor; the resulting receptor dimers must have a relative orientation between receptor chains that leads to productive interaction between the receptor cytoplasmic domains and their associated signaling molecules; and it might also be important that the activating ligand has a sufficiently slow dissociation rate such that the lifetime of the activated receptor complexes exceeds the threshold required for effective signaling to occur." (see Whitty at paragraph bridging pages R108-109).

Thus, there are a great number of considerations that make the production of a synthetic small molecule agonist that works by dimerization of membrane bound polypeptide chains, such as ligand induced dimerization of a cytokine receptor chains, unpredictable. However, the situation is even more unpredictable for CD52 given that in light of the knowledge in the art of agonizing CD52 with anti-CD52 antibodies as described in the preceding paragraphs, it seems most likely that ligands which form higher order ligand-CD52 complexes of not yet determined stoichiometry will ultimately be required to agonize CD52.

In conclusion, the instant claims encompass an invention of tremendous breadth, and essentially call for trial and error by the skilled artisan to begin discovering how to use the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge in the art. Reasonable correlation must exist between the scope of the claims and scope of

enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 12-15, 17, 18 and 20-22 are rejected under 35 U.S.C. 102(a)/(e) as being anticipated by Junichi Masuyama (US 2003/0064067) as evidenced by the instant specification at page 10, last paragraph and Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

As a preliminary matter it is noted that for the purposes of prior art examination the phrase "other than a 4C8 antibody" recited in claim 12 will be interpreted to mean "other than the particular 4C8 mAb described in Masuyama et al. (Masuyama, J. et al., (2002) J. Immunol., 169, 3710)."

Masuyama teaches a method for inducing differentiation and/or promoting proliferation of a regulatory T cell, comprising allowing CD3 agonists and 4C8 antigen agonists to act on immunocytes wherein a "4C8 antigen agonist" is "a substance which can induce…differentiation of the cells into regulatory T cells…[and/or]…proliferation of the cells maintaining the properties of regulatory T cells. The 4C8 antigen agonists include

natural ligands for 4C8 antigens, and antibodies against the 4C8 antigens. A specific example of the antibody is an anti-4C8 antibody produced by a hybridoma JM-1 (accession No. FERM BP-7757) that was deposited on Sep. 26, 2001 at the International Patent Organism Depositary (IPOD), National Institute of Advanced Industrial Science and Technology, Japan (1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan). Antibodies which can be used in the present invention are not limited to the above anti-4C8 antibody. According to the report of Masuyama et al. (Masuyama, J. et al., 1999. J. Exp. Med. 189:979-989; WO99/12972), antibodies having the function as a 4C8 antigen agonist can be obtained by screening monoclonal antibodies collected from animals immunized with human T cells using as an index the inhibition of in vitro extravascular migration of T cells." (See Masuyama at page 3, paragraph [0043]).

Masuyama also teaches humanized antibodies having the function as a 4C8 antigen agonist, practicing the methods of the invention on peripheral blood, lymph node or thymic immunocytes and the use of OKT3 as a CD3 agonist (see, e.g., page 4, paragraph [0045] and claims 2 and 7).

As evidenced by the instant specification at page 10, last paragraph, the 4C8 antigen is a CD52 molecule.

Thus, the "4C8 antigen agonists" of Masuyama are inherently CD52 agonists.

Furthermore, while Masuyama does not explicitly state that the regulatory T cell produced by their method have antigen-selective suppressive activity, this is an inherent property of cells generated with immobilized anti-CD52 and in the presence of a superantigen, as evidenced by the teachings of Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59, see in particular, column bridging paragraph on page 253 and 257). More particularly, given that the SEB superantigen of Watanabe can stimulate CD4+ TCR signaling as a stand-alone agent, as does immobilized anti-CD3 antibody, immobilized anti-CD3 antibody stimulation of CD4+ TCR in the presence of immobilized anti-CD52, like SEB superantigen stimulation of CD4+ TCR in the presence of immobilized anti-CD52, will also induce regulatory T-cells with antigen-selective suppressive activity.

Accordingly, Masuyama, as evidenced by the instant specification and Watanabe, anticipates the instant claims.

11. Claims 12-18 and 20-22 are rejected under 35 U.S.C. 102(b) as anticipated by Rowan et al. (Int Immunol. 1995 Jan;7(1):69-77, cited previously) as evidenced by the instant specification at page 10, last paragraph and Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59).

Rowan teaches a method for inducing differentiation and/or promoting proliferation of T cells comprising (a) isolating CD4+ T cells and (b) culturing said T cells of step (a) on a plate

to which the CAMPATH-1H antibody and the murine anti-CD3 antibody OKT3 have been immobilized (see, e.g., page 72, right column, 1st paragraph and materials and methods).

While it is noted that Rowan is silent about inducing differentiation and/or promoting proliferation of a regulatory T cell, Rowan nevertheless teaches a method comprising the same elements and steps as claimed and thus Rowan anticipates the instant claims. It is not apparent that the language or limitations of the instant claims result in a manipulative difference in the method steps when compared to the prior art disclosure.

Furthermore, while Rowan is silent about inducing differentiation and/or promoting proliferation of a regulatory T cell with antigen-selective suppressive activity, this is an inherent property of cells generated with immobilized anti-CD52 and in the presence of a superantigen, as evidenced by the teachings of Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59, see in particular, column bridging paragraph on page 253 and 257). More particularly, given that the SEB superantigen of Watanabe can stimulate CD4+ TCR signaling as a stand-alone agent, as does immobilized anti-CD3 antibody, immobilized anti-CD3 antibody stimulation of CD4+ TCR in the presence of immobilized anti-CD52, like SEB superantigen stimulation of CD4+ TCR in the presence of immobilized anti-CD52, will also induce regulatory T-cells with antigen-selective suppressive activity.

Accordingly, Rowan anticipates the instant claims as evidenced by the instant specification and Watanabe.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junichi Masuyama (US 2003/0064067) in view of Bluestone et al. (U.S. Patent No. 6,491,916).

The teachings of Masuyama are given above.

Masuyama differs from the claimed invention in that Masuyama does not explicitly teach the use of a humanized anti-CD3 antibody in the claimed method.

However, as taught by Bluestone the murine anti-CD3 OKT3 antibody and the humanized version of said antibody have equivalent biological properties (see Bluestone paragraph bridging columns 32-33).

Given the art recognized equivalence of these antibodies it would have been prima facie

obvious to one of ordinary skill in the art to substitute the humanized OKT3 anti-CD3 antibody of Bluestone for the murine OKT3 anti-CD3 antibody or Masuyama. The substitution of one art recognized equivalent element for another to yield a predictable result is prima facie obvious. See MPEP § 2144.06 and KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007).

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rowan et al. (Int Immunol. 1995 Jan;7(1):69-77, cited previously) in view of Bluestone et al. (U.S. Patent No. 6,491,916).

The teachings of Rowan are given above.

Rowan differs from the claimed invention in that Rowan does not explicitly teach the use of a humanized anti-CD3 antibody in the claimed method.

However, as taught by Bluestone, the murine anti-CD3 OKT3 antibody and the humanized version of said antibody have equivalent biological properties (see Bluestone paragraph bridging columns 32-33).

Given the art recognized equivalence of these antibodies it would have been prima facie obvious to one of ordinary skill in the art to substitute the humanized OKT3 anti-CD3 antibody of Bluestone for the murine OKT3 anti-CD3 antibody or Rowan. The substitution of one art recognized equivalent element for another to yield a predictable result is prima facie obvious. See MPEP § 2144.06 and KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007).

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because

the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 12-15 and 17-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/122,432 to Masuyama (US 2003/0064067) in view of Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59), Bluestone (U.S. Patent No. 6,491,916) and the instant specification at page 10, last paragraph.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference claims anticipate the instant claims.

It is noted that for the purposes of prior art examination the phrase "other than a 4C8 antibody" recited in claim 12 will be interpreted to mean "other than the particular 4C8 mAb described in Masuyama et al. (Masuyama, J. et al., (2002) J. Immunol., 169, 3710)."

The reference claims differ from the claimed invention in not reciting the use of an anti-CD52 agonist, the use of humanized anti-CD3 or that the regulatory T cells have antigen-selective suppressive activity.

However, as evidenced by the instant specification at page 10, last paragraph, the 4C8 antigen is a CD52 molecule.

Thus, the "4C8 antigen agonists" of Masuyama are inherently CD52 agonists.

Moreover, as taught by Bluestone the murine anti-CD3 OKT3 antibody and the humanized version of said antibody have equivalent biological properties (see Bluestone paragraph bridging columns 32-33).

Given the art recognized equivalence of these antibodies it would have been prima facie obvious to one of ordinary skill in the art to substitute the humanized OKT3 anti-CD3 antibody of Bluestone for the murine OKT3 anti-CD3 antibody or Masuyama. The

substitution of one art recognized equivalent element for another to yield a predictable result is prima facie obvious. See MPEP § 2144.06 and KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007).

Furthermore, while Masuyama does not explicitly state that the regulatory T cell produced by their method have antigen-selective suppressive activity, this is an inherent property of cells generated with immobilized anti-CD52 and in the presence of a superantigen, as evidenced by the teachings of Watanabe et al. (Clin Immunol. 2006 Sep;120(3):247-59, see in particular, column bridging paragraph on page 253 and 257). More particularly, given that the SEB superantigen of Watanabe can stimulate CD4+ TCR signaling as a stand-alone agent, as does immobilized anti-CD3 antibody, immobilized anti-CD3 antibody stimulation of CD4+ TCR in the presence of immobilized anti-CD52, like SEB superantigen stimulation of CD4+ TCR in the presence of immobilized anti-CD52, will also induce regulatory T-cells with antigen-selective suppressive activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
June 13, 2008

/Michail A Belyavskyi/
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